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Search Results -

Terms	Documents
L3 and L5	8

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Search: L7

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Search History

DATE: Wednesday, August 24, 2005 Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT; PLUR=YES; OP=AND			
L7	l3 and l5	8	L7
L6	l4 and L5	348	L6
L5	cardiomyocyte or myocardium	12773	L5
L4	l1 and l2	759	L4
L3	l1 with L2	10	L3
L2	(infus$ or inject$) near7 (artery or coronary adj (artery or sinus))	5520	L2
L1	adeno-associated near3 vector or aav	8706	L1

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 10 of 10 returned.

1. 20050107323. 28 May 04. 19 May 05. Cardiac arrhythmia treatment methods. Donahue, J. Kevin, et al. 514/44; 424/93.2 536/23.5 A61K048/00 C07H021/04.

2. 20040266717. 28 May 04. 30 Dec 04. Cardiac arrhythmia treatment methods. Donahue, J. Kevin, et al. 514/44; A61K048/00.

3. 20040266716. 28 May 04. 30 Dec 04. Cardiac arrhythmia treatment methods. Donahue, J. Kevin, et al. 514/44; A61K048/00.

4. 20040254134. 10 Aug 04. 16 Dec 04. Biological pacemaker. Marban, Eduardo, et al. 514/44; 424/93.21 A61K048/00.

5. 20040009151. 01 Apr 03. 15 Jan 04. Methods for delivering recombinant adeno-associated virus virions to the liver of a mammal. Kay, Mark A., et al. 424/93.2; 435/456 A61K048/00 C12N015/861.

6. 20030072744. 18 Sep 02. 17 Apr 03. Methods of altering cardiac cell phenotype. Engler, Robert L.. 424/93.21; 514/44 A61K048/00.

7. 20020155101. 06 Sep 01. 24 Oct 02. Cardiac arrhythmia treatment methods. Donahue, J. Kevin, et al. 424/93.21; 435/6 514/44 C12Q001/68 A61K048/00.

8. 20020106381. 13 Jun 01. 08 Aug 02. Methods for administering recombinant adeno-associated virus virions to humans previously exposed to adeno-associated virus. High, Katherine A.. 424/233.1; 424/93.21 A61K048/00 A61K039/235.

9. 20010016193. 19 Dec 00. 23 Aug 01. Methods of altering cardiac cell phenotype. Engler, Robert L.. 424/93.21; 435/320.1 A61K048/00.

10. 6162796. 27 Sep 95; 19 Dec 00. Method for transferring genes to the heart using AAV vectors. Kaplitt; Michael G., et al. 514/44; 435/320.1 435/325 435/455 435/456. A61K031/70.

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Terms	Documents
L1 with L2	10

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Search Results - Record(s) 1 through 8 of 8 returned.

1. 20050107323. 28 May 04. 19 May 05. Cardiac arrhythmia treatment methods. Donahue, J. Kevin, et al. 514/44; 424/93.2 536/23.5 A61K048/00 C07H021/04.

2. 20040266717. 28 May 04. 30 Dec 04. Cardiac arrhythmia treatment methods. Donahue, J. Kevin, et al. 514/44; A61K048/00.

3. 20040266716. 28 May 04. 30 Dec 04. Cardiac arrhythmia treatment methods. Donahue, J. Kevin, et al. 514/44; A61K048/00.

4. 20040254134. 10 Aug 04. 16 Dec 04. Biological pacemaker. Marban, Eduardo, et al. 514/44; 424/93.21 A61K048/00.

5. 20030072744. 18 Sep 02. 17 Apr 03. Methods of altering cardiac cell phenotype. Engler, Robert L.. 424/93.21; 514/44 A61K048/00.

6. 20020155101. 06 Sep 01. 24 Oct 02. Cardiac arrhythmia treatment methods. Donahue, J. Kevin, et al. 424/93.21; 435/6 514/44 C12Q001/68 A61K048/00.

7. 20020106381. 13 Jun 01. 08 Aug 02. Methods for administering recombinant adeno-associated virus virions to humans previously exposed to adeno-associated virus. High, Katherine A.. 424/233.1; 424/93.21 A61K048/00 A61K039/235.

8. 20010016193. 19 Dec 00. 23 Aug 01. Methods of altering cardiac cell phenotype. Engler, Robert L.. 424/93.21; 435/320.1 A61K048/00.

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Terms	Documents
L3 and L5	8

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=> d his

(FILE 'HOME' ENTERED AT 18:16:44 ON 24 AUG 2005)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH, LIFESCI' ENTERED AT 18:17:04 ON 24 AUG 2005

L1 8447 S ADENO-ASSOCIATED(W)VECTOR OR AAV
L2 28989 S (INFUS? OR INJECT?)(7A)(ARTERY OR CORONARY(W)(ARTERY OR SINUS
L3 36 S L1 AND L2
L4 279837 S CARDIOMYOCYTE OR MYOCARDIUM
L5 11 S L3 AND L4
L6 16 DUP REM L3 (20 DUPLICATES REMOVED)
L7 3 DUP REM L5 (8 DUPLICATES REMOVED)

=> d au ti so pi ab 1-16 16

L6 ANSWER 1 OF 16 MEDLINE on STN DUPLICATE 1
AU Kaspar Brian K; Roth David M; Lai N Chin; Drumm Jeffrey D; Erickson Dawn A; McKirnan M Dan; Hammond H Kirk
TI Myocardial gene transfer and long-term expression following intracoronary delivery of adeno-associated virus.
SO journal of gene medicine, (2005 Mar) 7 (3) 316-24.
Journal code: 9815764. ISSN: 1099-498X.
AB Adeno-associated viral vectors (**AAV**) can direct long-term gene expression in post-mitotic cells. Previous studies have established that long-term cardiac gene transfer results from intramuscular injection into the heart. Cardiac gene transfer after direct intracoronary delivery of **AAV** in vivo, however, has been minimal in degree, and indirect intracoronary delivery, an approach used in an increasing number of studies, appears to be receiving more attention. To determine the utility of indirect intracoronary gene transfer of **AAV**, we used aortic and pulmonary **artery** cross clamping followed by proximal aortic **injection** of **AAV** encoding enhanced green fluorescent protein (**AAV**.EGFP) at 10(11) DNase resistant particles (drp; high-performance liquid chromatography (HPLC)-purified) per rat. Gene expression was quantified by fluorescent microscopy at four time points up to 1 year after vector delivery, revealing 20-32% transmural gene expression in the left ventricle at each time point. Histological analysis revealed little or no inflammatory response and levels of transgene expression were low in liver and undetectable in lung. In subsequent studies in pigs, direct intracoronary delivery into the left circumflex coronary artery of **AAV**.EGFP (2.64-5.28 x 10(13) drp; HPLC-purified) resulted in gene expression in 3 of 4 pigs 8 weeks following injection with no inflammatory response in the heart. PCR analysis confirmed **AAV** vector presence in the left circumflex perfusion bed. These data indicate that intracoronary delivery of **AAV** vector is associated with transgene expression in the heart, providing a means to obtain long-term expression of therapeutic genes. Copyright (c) 2004 John Wiley & Sons, Ltd.

L6 ANSWER 2 OF 16 MEDLINE on STN DUPLICATE 2
AU Ohashi Kazuo; Nakai Hiroyuki; Couto Linda B; Kay Mark A
TI Modified infusion procedures affect recombinant adeno-associated virus vector type 2 transduction in the liver.
SO Human gene therapy, (2005 Mar) 16 (3) 299-306.
Journal code: 9008950. ISSN: 1043-0342.
AB Recombinant adeno-associated virus (rAAV) vectors have therapeutic potential for the treatment of several types of liver diseases including hepato-deficiency disorders. Most of the preclinical and clinical applications involve the use of **adeno-associated vector** serotype 2 (**AAV**-2). However, when this vector is delivered at high doses into the portal vein or hepatic artery, a

relatively small number of hepatocytes are stably transduced. We elected to determine if the route of vector administration and altering the vascular delivery route within the liver influenced the relative level of transduction. First, we delivered an **AAV** vector expressing the human factor IX gene from a liver-specific promoter into the hepatic artery, portal vein, or general circulation of rats. Transgene expression was equal with hepatic **artery** and portal vein **infusion** , which was higher than vector administered via peripheral venous infusion. Next, we determined how localized perfusion or changing the vector dwell time affected **AAV** transduction in vivo. To do this, we infused an **AAV** vector lacking a functional expression and quantified transduction by quantifying the number of double-stranded vector DNA genomes. By increasing vector dwell time in the liver to 5 min, vector transduction was enhanced approximately 4- to 5- fold. To establish if gene transduction could be restricted to a specific anatomic location in the liver, we delivered vector into specific liver lobes by clamping the venous inflow to the middle and left liver lobes (noninfused lobes) and infusing vector into the right two liver lobes through the hepatic artery followed by vector circulation between the two right lobes and general circulation for 5 min. With this selective infusion, 40 to 120 times higher vector genome was observed in the perfused lobes than the nonperfused lobes. All the procedures described in this study were performed without detectable liver injury or toxicity. In all, the present study clearly demonstrated that hepatic arterial infusion of rAAV is effective for liver-directed gene therapy and that other parameters related to blood flow can be adjusted to further optimize gene transfer.

L6 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN
IN Kay, Mark A.; High, Katherine A.; Couto, Linda B.
TI Methods for delivering recombinant adeno-associated virus virions to the liver of a mammal
SO U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004009151	A1	20040115	US 2003-405047	20030401

AB Methods for introducing recombinant adeno-associated virus (rAAV) virions into the liver of a mammal are provided. In these methods, the liver is partially or completely isolated from its blood supply, a catheter is introduced into the liver via a peripheral blood vessel, and rAAV virions are then infused through the catheter to the liver. The methods described herein may be used, for example, to deliver heterologous genes encoding therapeutic proteins to the hepatocytes of humans. This can be accomplished, for example, by introducing the catheter into a femoral artery, threading the catheter into the hepatic **artery**, and **infusing** rAAV virions through the catheter and into the liver. Exemplary examples of heterologous genes include those coding for blood coagulation factors. A study is described demonstrating that **AAV** -factor IX delivered via hepatic **artery infusion** in human with hemophilia B can transduce hepatocytes and lead to expression of therapeutic levels of factor IX.

L6 ANSWER 4 OF 16 MEDLINE on STN DUPLICATE 3
AU Chu Danny; Sullivan Christopher C; Du Lingling; Cho Augustine J; Kido Masakuni; Wolf Paul L; Weitzman Matthew D; Jamieson Stuart W; Thistlethwaite Patricia A
TI A new animal model for pulmonary hypertension based on the overexpression of a single gene, angiopoietin-1.
SO Annals of thoracic surgery, (2004 Feb) 77 (2) 449-56; discussion 456-7.
Journal code: 15030100R. ISSN: 0003-4975.
AB BACKGROUND: Angiopoietin-1 gene expression in human pulmonary hypertensive lungs is directly proportional to increasing pulmonary vascular resistance. We hypothesized that targeted overexpresssion of

angiopoietin-1 in the lung would cause persistent pulmonary hypertension in an animal model. METHODS: We injected 2 x 10(10) genomic particles of adeno-associated virus-angiopoietin-1 (**AAV**-Ang-1) into the right ventricular outflow tract of 30 Fischer rats while using adeno-associated virus-lacZ (**AAV**-lacZ) injected rats and carrier-injected rats as our control groups. All animals underwent survival surgery and were sacrificed at serial timepoints postgene delivery. At each timepoint, pulmonary artery pressures were measured and pulmonary angiography using the Microfil polymer perfusion technique was performed. The lungs were harvested for pathologic analysis, mRNA analysis, Western blot assays, and in situ RNA hybridization to localize gene expression. RESULTS: Pulmonary **artery** pressures of **AAV**-Ang-1 **injected** rats were significantly increased compared with the control groups ($p < 0.01$) at all timepoints. Pathologic analysis of **AAV**-Ang-1 lung specimens demonstrated increased smooth muscle cell proliferation within the medial layer of arterioles with obliteration of small vessels similar to that seen in human pulmonary hypertension. Angiograms of **AAV** -Ang-1 injected lungs showed blunting of small peripheral arterioles consistent with advanced pulmonary hypertension. In situ RNA hybridization localized angiopoietin-1 expression to the vascular wall of small-caliber pulmonary vessels. Protein and mRNA assays confirmed persistent angiopoietin-1 expression in the lung for up to 60 days postgene delivery. CONCLUSIONS: Overexpression of angiopoietin-1 using an adeno-associated virus vector causes pulmonary hypertension in rats. These data provide a novel physiologic animal model for pulmonary hypertension.

L6 ANSWER 5 OF 16 MEDLINE on STN DUPLICATE 4
AU Iwatate M; Gu Y; Dieterle T; Iwanaga Y; Peterson K L; Hoshijima M; Chien K R; Ross J
TI In vivo high-efficiency transcoronary gene delivery and Cre-LoxP gene switching in the adult mouse heart.
SO Gene therapy, (2003 Oct) 10 (21) 1814-20.
Journal code: 9421525. ISSN: 0969-7128.
AB High-efficiency somatic gene transfer in adult mouse heart has not yet been achieved in vivo. Here, we demonstrate high-efficiency in vivo transcoronary gene delivery to the adult murine myocardium using a catheter-based technique with recombinant adenovirus (AdV) and adeno-associated virus (**AAV**) vectors in normal and genetically engineered mice. The method involves immersion hypothermia followed by transient aortic and pulmonary **artery** occlusion with proximal intra-aortic segmental **injection** of cardioplegic solution containing substance P and viral vectors. Gene expression measured using a LacZ marker gene was observed throughout both ventricles. The expression efficiency of a cytoplasmic LacZ marker gene in the left ventricular myocardium was 56.4+/-14.5% (mean+/-s.d.) at 4 days with an AdV vector, and with an **AAV** vector it was 81.0+/-5.9% at 4 weeks. Following **AAV** gene transfer, no gene expression was found in kidney, brain, lung, and spleen, but there was slight expression in liver. In addition, we demonstrate temporally controlled genetic manipulation in the heart with an efficiency of 54.6+/-5.2%, by transferring an AdV vector carrying Cre recombinase in ROSA26 flox-LacZ reporter mice. Procedure-related mortality was 16% for AdV and zero for **AAV** transfer. Thus, this method provides efficient, relatively homogeneous gene expression in both ventricles of the adult mouse heart, and offers a novel approach for conditional gene rescue or ablation in genetically engineered mouse models.

L6 ANSWER 6 OF 16 MEDLINE on STN DUPLICATE 5
AU Li J; Wang D; Qian S; Chen Z; Zhu T; Xiao X
TI Efficient and long-term intracardiac gene transfer in delta-sarcoglycan-deficiency hamster by adeno-associated virus-2 vectors.
SO Gene therapy, (2003 Oct) 10 (21) 1807-13.

Journal code: 9421525. ISSN: 0969-7128.

AB Intracardiac gene transfer and gene therapy have been investigated with different vector systems. Here we used adeno-associated virus (**AAV**) vectors to deliver either a reporter gene or a therapeutic gene into the heart of golden Syrian hamsters. The method of gene delivery was direct **infusion** of the AAV2 vectors into the **coronary artery** ex vivo in a heterotopically transplanted heart. When an AAV2 vector carrying the Lac-Z gene driven by CMV promoter was delivered into the heart of healthy hamsters, effective gene transfer was achieved in up to 90% of the cardiomyocytes. Lac-Z gene expression persisted for more than 1 year without immune rejection or promoter shutoff. Furthermore, when an AAV2 vector carrying human delta-sarcoglycan gene was similarly delivered into the heart of Bio14.6 Syrian hamster, a congestive heart failure and limb girdle muscular dystrophy animal model, widespread therapeutic gene transfer was achieved in a majority of the cardiomyocytes. Efficient expression of the human delta-sarcoglycan gene in the dystrophic hamster hearts restored the entire sarcoglycan complex that was missing due to the primary deficiency of delta-sarcoglycan. Transgene expression persisted for 4 months (the duration of the study) without immune rejection or promoter shutoff. These results indicate that **AAV** is a promising vector system for cardiac gene therapy.

L6 ANSWER 7 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AU High, Katherine A. [Reprint Author]; Manno, Catherine S. [Reprint Author]; Sabatino, Denise E. [Reprint Author]; Hutchison, Sylvia; Dake, Michael; Razavi, Mahmood; Kaye, Robin [Reprint Author]; Arruda, Valder R. [Reprint Author]; Herzog, Roland W. [Reprint Author]; Rustagi, Pradip K.; Rasko, John E. J.; Hoots, Keith; Blatt, Phillip; Sommer, Jurg; Leonard, Deborah D. B.; Addya, Kathakali; Ragni, Margaret V.; Ozelo, Margareth; Konkle, Barbara A. [Reprint Author]; Lessard, Ruth; Axsom, Kelly M. [Reprint Author]; Chew, Amy J.; Glader, Bertil; Pierce, Glenn; Couto, Linda B.; Kay, Mark A.

TI Immune responses to **AAV** and to Factor IX in a Phase I study of **AAV**-mediated, liver-directed gene transfer for hemophilia B.

SO Blood, (November 16 2003) Vol. 102, No. 11, pp. 154a-155a. print. Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology. CODEN: BLOOAW. ISSN: 0006-4971.

AB Studies in mice, hemophilic dogs, and non-human primates have shown long-term expression of Factor IX (F.IX) after administration of a recombinant **AAV** vector expressing F.IX into the portal vein or hepatic artery. Specifically, portal vein or hepatic **artery infusion** of apprx1X1012 vg/kg **AAV** vector expressing canine F.IX in hemophilic dogs showed sustained (>3 years) circulating levels of F.IX in the range of 4-12% (Blood 99:2670). To determine whether hepatic **artery infusion** of **AAV**-F.IX could result in a similar outcome in humans with severe hemophilia B, a Phase I dose escalation study was initiated. To date, six subjects have been studied at doses ranging from 8X1010 to 2X1012 vg/kg. All subjects have severe hemophilia B and all were HCV antibody positive. The 4 subjects treated in the first two dose cohorts showed no vector-related toxicity but also failed to achieve F.IX levels above baseline. In all subjects tested so far, DNA extracted from semen has been transiently positive for vector sequences, with all subjects negative at this time. None of the six subjects have developed inhibitors to F.IX. Subject E, the first to receive a dose of 2X1012 vg/kg, showed circulating F.IX levels in the range of 5-12%, which persisted for 5 wks and then gradually fell to the baseline of <1%. Concomitant with the fall in F.IX level was a rise in transaminase levels, first noted 4 weeks after injection, peaking at apprx9X normal at 5 wks, then returning to normal. This subject had low baseline anti-**AAV** antibody titers (1:2). Subject F, also treated at 2X1012 vg/kg, had higher (1:17) baseline anti-

AAV antibody titers, and demonstrated only short-lived, low level F.IX expression (1-3%X2 weeks), but no transaminitis. To assess the role of the immune response in this setting, PBMCs from subjects E and F were incubated with peptides derived from the **AAV**-2 capsid sequence and from the wild-type hF.IX sequence. IFN-gamma secretion was measured in ELISPOT assays, which showed, in subject E, a 10-fold elevation in IFN-gamma compared to media control at the 4 wk time point following incubation with one of the **AAV** peptide pools. All other time points in subjects E and F were negative with all peptide pools tested. We conclude that: 1) **AAV**-F.IX can transduce human hepatocytes in vivo, resulting in therapeutic circulating factor levels; 2) the vector dose required to achieve a therapeutic factor level was accurately predicted by animal models; 3) the transient nature of expression in Subject E was not predicted by earlier studies in animal models; 4) differences in peak levels achieved in subjects E and F suggest that pre-existing antibodies to **AAV**-2 may block transduction when vector is administered systemically. Additional clinical studies currently underway will assess whether F.IX expression can be achieved at a lower vector dose (1.2X1012vg/kg), and whether specific immune responses to either **AAV** or F.IX limit duration of expression in **AAV**-mediated, liver-directed gene transfer in humans.

L6 ANSWER 8 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AU Andreeff, Michael [Reprint Author]; Studeny, Matus [Reprint Author]; Dembinski, Jennifer [Reprint Author]; Cabreira-Hansen, Maria [Reprint Author]; Zompetta, Claudia [Reprint Author]; Champlin, Richard E. [Reprint Author]; Chada, Sunil; Lang, Frederick F. Jr.; Marini, Frank C. III [Reprint Author]

TI Mesenchymal progenitor cells as gene delivery systems for cancer and leukemia therapy.

SO Blood, (November 16 2003) Vol. 102, No. 11, pp. 60a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

AB We have previously demonstrated that bone marrow-derived non-hematopoietic stem cells (MSC) integrate into solid tumors as stromal fibroblasts following intravenous injection (Cancer Res 62:3603-3608, 2002). This finding suggests the development of novel anti-cancer therapies based on the local production of biological agents by gene-manipulated MSC. Here, we examined whether human MSC producing human interferon-beta (IFNbeta-MSC) can inhibit the growth of metastatic tumors in the lungs of SCID mice. MSC were transduced with an IFNb expressing adenoviral vector. These IFNbeta-MSC produced 40-50,000 I.U. of IFNbeta/106 cells/24 hours. IFNbeta-MSC directly inhibited the growth of both A375 melanoma and MDA 231 breast carcinoma cells in co-culture experiments in vitro. We then injected IFNbeta-MSC intravenously (IV) (four doses of 106 MSC/week) into SCID mice bearing established MDA-231 carcinomas in the lungs; tumor growth was inhibited as compared to untreated controls (p=0.0073). In contrast, when recombinant IFNbeta protein (50,000 IU every other day) was injected subcutaneously, no tumor inhibition was observed (p=0.14). IV injected IFNbeta-MSC prolonged the survival of mice bearing metastatic MDA 231 tumors as compared to untreated animals (p=0.001). Increased survival was found only when IFNbeta-MSC were injected IV, but not subcutaneously (p=0.021 versus p=0.4). Similar results were seen in a model of pulmonary metastases of A375 melanoma. MSC marked with beta-gal were found only in tumors, where they proliferated and incorporated BUdR, but not in normal tissues, except in bone marrow and spleen. Intraperitoneal injections of IFNbeta-MSC in mice carrying ovarian carcinomas resulted in doubling of survival (SKOV-3) and cures of 70% of mice carrying OVAR-3 tumors. MSC **injected** into the carotid **artery** (IA) of mice with gliomas selectively proliferated in the human glioma xenografts, not in normal brain tissues. Co-cultures of IFNbeta-MSC and glioma cells in vitro and intratumoral injection of IFNbeta-MSC in vivo significantly

inhibited growth of these tumors. In a model of chronic myelogenous leukemia in blast crisis (KBM5 cells), following **AAV** infection and regulated by mifepristone (RU486), interferon alpha (IFNalpha) produced in vivo by MSC induced tumor regressions and doubled the survival of scid mice. The melanoma differentiation-associated gene 7 (MDA7), a member of the IL-10 family with strong anti-cancer activity, expressed by AdV gene transfer in MSC, was found to preferentially inhibit Gleevec (STI571) resistant KBM5 cells. Data suggest that IV, IP or IA administered gene-modified MSC can inhibit the growth of leukemias, metastatic tumors of the lungs, ovarian and brain tumors. Importantly, the anti-tumor effects were only achieved when MSC were integrated into the tumor microenvironment, but not when MSC were injected subcutaneously or when recombinant protein was used. Therefore, tumor inhibition required spatial proximity of MSC to the malignant cells. These findings indicate that IFNalpha, IFNbeta and MDA7 can serve as direct inhibitors of malignant cell proliferation and suggest the use of gene-manipulated MSC for cancer and leukemia therapy.

L6 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN
IN McClelland, Alan; Allen, James
TI Improved muscle-directed gene transfer by use of recombinant **AAV** -1 and **AAV**-6 virions and its application in gene therapy
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002063025	A2	20020815	WO 2002-US3195	20020201
WO 2002063025	A3	20031106		
WO 2002063025	C1	20040521		

PI

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002159978	A1	20021031	US 2002-56788	20020123

AB Methods for using novel recombinant adeno-associated virus (rAAV) virion serotypes are disclosed. The methods enable an increase in transduction efficiency of rAAV virions in mammalian muscle cells or tissue. Specifically, the methods described herein employ rAAV-1 and rAAV-6 serotype virions to deliver heterologous nucleic acid mols. of interest to muscle cells or tissue of a mammal where rAAV-2 transduces poorly for readministration. The disclosed methods describe direct injection into muscle tissue, intravascular administration of rAAV virions, and limb perfusion to deliver heterologous nucleic acid mols. of interest to at least one muscle cell of a mammal. The disclosed methods also describe the treatment of hemophilia, using the rAAV virions of the invention, by administering the rAAV virions to a mammalian subject with hemophilia so that blood coagulation proteins, such as Factor VIII or Factor IX, are expressed at levels greater than those achieved using the rAAV-2 serotype.

L6 ANSWER 10 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN
AU Arruda, Valder R. [Reprint Author]; Schuettrumpf, Joerg; Couto, Linda; Leonard, Debra; Addya, Kathakali; Liu, Jian-hua; Sommer, Joerg; Herzog, Roland W.; Kay, Mark A.; Glader, Bert; Manno, Catherine S.; Chew, Amy; High, Katherine A.
TI Assessing the Risk of Inadvertent Germline Transmission of Vector DNA Following Intravascular Delivery of rAAV Vector.

SO Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 3425. print. Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

AB In pre-clinical experiments an **AAV** vector encoding cF.IX to the liver, has resulted in therapeutic levels of circulating F.IX (4-12%) in dogs with severe hemophilia B. A safety issue for in vivo gene transfer is the risk of inadvertent germline transmission of vector sequences. In dogs, following **AAV injection** (7x10e12 vg/kg) into the hepatic **artery** no vector sequences were detected by PCR when both gonadal tissue and semen samples were analyzed. However, when the first two human subjects in an **AAV**-FIX clinical trial were treated at a dose of 2 x 10e11 vg/kg, delivered via the hepatic artery, total semen samples were positive for vector sequences up to 10-12 weeks post-procedure. In contrast to dogs, New Zealand white rabbits injected intravenously with the clinical vector **AAV**-FIX16 demonstrated biodistribution similar to that seen in humans, with semen samples transiently positive for vector sequences in the period immediately following vector injection. Animals (n=27) were injected at doses ranging from 1 x 10e11 to 1 x 10e13 vg/kg and semen samples were collected weekly. DNA obtained from total semen, motile, and non-motile sperm fractions were assayed by the same sensitive PCR developed for the clinical trial. We found that rabbits uniformly showed a positive signal in serum at 7 days post injection. Moreover, there was a dose-dependent increase in the likelihood of finding vector sequences in semen DNA. Thus, animals injected at 1 x 10e11 vg/kg were initially positive but cleared by week 4 following injection. However, animals injected with a dose of 1 x 10e12 vg/kg or 1 x 10e13 vg/kg required 8- 13 weeks to clear. Semen fractions enriched for motile sperm were transiently positive and the clearance was faster than for total semen specimens. These data suggest that clearing of vector sequences from semen DNA eventually occurs and that the kinetics of clearing is dose-dependent. Findings from the clinical study are consistent with this hypothesis, since both subjects injected at the low dose of 2 x 10e11 vg/kg demonstrated clearing of PCR positivity in semen over a period of 10-12 weeks. In previous studies we have show that, **AAV**-2 vector disseminates to the gonads via hematogenous route and binds to heparan sulfate proteoglycan structures in the testis and it slowy degraded. FISH did not disclose vector signal in the germ cells. Here animals followed for more than 5 spermatogenesis cycles (200 days) do not reveal any subsequent recurrence of vector sequences in the semen, which suggests that no early spermatogonial precursors were affected by vector. Attempts to transduce mature motile spermatogonia from rabbits or humans in culture with an **AAV**-CMV-GFP vector failed to demonstrate transgene expression. We conclude that the risk of persistent positivity of semen DNA for vector sequences is low at the doses tested thus far. The rabbit model will allow detailed analysis of semen fractions over a series of time points. Recent work with alternate serotypes of **AAV** has established the potential utility of these vectors for gene transfer; since these alternate serotypes may use different receptors to gain entry to the cell, it will be necessary to perform additional studies to assess the likelihood of germline transmission in these settings.

L6 ANSWER 11 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AU Kay, Mark A. [Reprint Author]; High, Katherine [Reprint Author]; Glader, Bertil [Reprint Author]; Manno, Catherine S. [Reprint Author]; Hutchinson, Sylvia [Reprint Author]; Dake, Mike [Reprint Author]; Razavi, Mahmood [Reprint Author]; Kaye, Robin [Reprint Author]; Arruda, Valder R. [Reprint Author]; Herzog, Roland [Reprint Author]; McClelland, Alan [Reprint Author]; Rustagi, Pradip [Reprint Author]; Johnson, Fred [Reprint Author]; Rasko, John E. J [Reprint Author]; Hoots, Keith [Reprint Author]; Blatt,

Phillip [Reprint Author]; Leonard, Debra G. B. [Reprint Author]; Addya, Kathakali [Reprint Author]; Konkle, Barbara [Reprint Author]; Chew, Amy [Reprint Author]; Couto, Linda [Reprint Author]

TI A Phase I/II Clinical Trial for Liver Directed **AAV**-Mediated Gene Transfer for Severe Hemophilia B.

SO Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 426. print. Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

AB Hemophilia is an inherited bleeding disorder that is due to the absence of functional Factors VIII or IX. We have completed pre-clinical studies of **AAV**-mediated gene transfer of the Factor IX (F.IX) gene in animal models prior to initiating trials in human subjects with severe hemophilia B. A Phase I trial of **AAV**-mediated F.IX gene transfer to skeletal muscle showed that vector administration at doses up to 1.8 x 10e12 vg/kg was safe and that skeletal muscle transduction was similar in humans and in animal models. Gene transfer and expression were demonstrated in all 8 subjects treated and persisted for at least 10 months post-injection (last time point biopsied). In animal studies, liver-directed gene transfer has a 10-50 fold dose advantage and reduced probability of forming inhibitors when compared to muscle delivery. With vector administration into the liver, preclinical efficacy studies have demonstrated a life-long correction of the bleeding diathesis in hemophilia B mice, and reconstitution of up to 14% of wildtype levels of canine F.IX in hemophilic dogs. To date, one of the treated hemophilia B dogs followed for >4 years still maintains the initial level of F.IX following the administration of **AAV**-2. As a result, a number of preclinical safety studies of **AAV** into the liver of various species were performed to generate the appropriate safety data to support a clinical trial. The study design includes two subjects at a low dose (2 x 10e11 vg/kg), and up to four subjects each at a middle (1 x 10e12 vg/kg) and high dose (5 x 10e12 vg/kg). Subjects are infused with an **AAV**-2 vector containing a F.IX minigene and liver specific promoter with an intrahepatic **artery injection**. The mid-dose group in the clinical trial will receive a dose that corresponds to the dose that resulted in 4 to 14% plasma F.IX levels in hemophilia B dogs. To participate in this trial, adult males with severe hemophilia B who were HCV infected with circulating HCV RNA underwent liver biopsy to determine degree of hepatic fibrosis. Subjects could participate if hepatic fibrosis < Grade 2 on the Poynard scale. Three subjects had liver biopsies prior to participation. To date, both of the low dose and two of the mid-dose subjects have been infused with vector. All 4 subjects tolerated the procedure without incident, and the blood chemistries including the liver enzymes and blood counts remained normal after treatment. In the first two subjects, followed for 12 and 8 months respectively, small amounts of vector DNA were transiently detected in body fluids including the semen. Coagulation parameters including plasma F.IX levels remained unchanged in the low-dose group. Because 6-8 weeks is required to reach plateau levels of transgene expression, the efficacy results for the mid-dose group are not yet available. We conclude that hepatic artery administration of recombinant **AAV**-F.IX to humans at doses up to 1 x 10e12 vg/kg was well-tolerated with no acute toxicity. Assessment of efficacy and of long-term effects will require further observation.

L6 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2005 ACS on STN

IN Couto, Linda B.; Colosi, Peter C.; Qian, Xiaobing

TI Adeno-associated virus vectors for expression of factor VIII by target cells

SO U.S., 43 pp., Cont.-in-part of U.S. Ser. No. 364,862.
CODEN: USXXAM

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	US 6200560	B1	20010313	US 1999-470618	19991222
	US 6221349	B1	20010424	US 1999-364862	19990730
	US 2001010815	A1	20010802	US 2000-740211	20001218
	WO 2001045510	A1	20010628	WO 2000-US34925	20001221
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 2002159977	A1	20021031	US 2001-7968	20011116
	US 2003099618	A1	20030529	US 2002-293400	20021112

AB The present invention provides improved viral vectors useful for the expression of genes at high levels in human cells. In particular, the present invention provides recombinant **adeno-assocd**. **vectors** (**AAV**) suitable for gene therapy. These vectors are capable of delivering nucleic acid containing constructs which result in the production of full-length therapeutic levels of biol. active Factor VIII in the recipient individual in vivo. The present invention also provides pharmaceutical compns. comprising such **AAV** vectors, as well as methods for making and using these constructs.

L6 ANSWER 13 OF 16 MEDLINE on STN DUPLICATE 6

AU Arruda V R; Fields P A; Milner R; Wainwright L; De Miguel M P; Donovan P J; Herzog R W; Nichols T C; Biegel J A; Razavi M; Dake M; Huff D; Flake A W; Couto L; Kay M A; High K A

TI Lack of germline transmission of vector sequences following systemic administration of recombinant **AAV**-2 vector in males.

SO Molecular therapy : journal of the American Society of Gene Therapy, (2001 Dec) 4 (6) 586-92.
Journal code: 100890581. ISSN: 1525-0016.

AB A potential consequence of systemic administration of viral vectors is the inadvertent introduction of foreign DNA into recipient germ cells. To evaluate the safety of in vivo recombinant adeno-associated virus (rAAV) mediated gene transfer approaches for hemophilia B, we explored the risk of germline transmission of vector sequences following intramuscular (IM) injection of rAAV in four species of male animals (mouse, rat, rabbit and dog). In vector biodistribution studies in mice and rats, there is a dose-dependent increase in the likelihood that vector sequences can be detected in gonadal DNA using a sensitive PCR technique. However, in dogs DNA extracted from semen is negative for vector sequences. To address this discrepancy, studies were done in rabbits, and both semen and testicular DNAs were analyzed for the presence of vector sequences. These studies showed that no **AAV** vector sequences were detected in DNA extracted from rabbit semen samples collected at time points ranging from 7 to 90 days following IM injection of 1 x 10(13) vector genomes rAAV (vg) per kg. In contrast, DNA extracted from gonadal tissue was positive for vector sequences, but the positive signals diminished in number and strength with time. By FISH analysis, **AAV** signals were localized to the testis basement membrane and the interstitial space; no intracellular signal was observed. We observed similar findings following hepatic artery administration of rAAV in rats and dogs, suggesting that our findings are independent of the route of administration of vector. Attempts to transduce isolated murine spermatogonia directly with **AAV**-lacZ were unsuccessful. In clinical studies human subjects injected IM with an **AAV** vector at doses up to 2 x 10(12) vg/kg have shown no evidence of vector sequences in semen. Together, these studies suggest that rAAV introduced into skeletal muscle or the hepatic artery does not transduce male germ cells efficiently. We conclude that

the risk of inadvertent germline transmission of vector sequences following IM or hepatic **artery injection** of **AAV**-2 vectors is extremely low.

L6 ANSWER 14 OF 16 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN

AU Nakai, Hiroyuki [Reprint author]; Ohashi, Kazuo [Reprint author]; Arruda, Valder; McClelland, Alan; Couto, Linda B.; Meuse, Leonard [Reprint author]; Storm, Theresa [Reprint author]; Dake, Michael D.; Manno, Catherine S.; Glader, Bertil [Reprint author]; High, Katherine A.; Kay, Mark A. [Reprint author]

TI A proposed rAAV-liver directed clinical trial for hemophilia B.

SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 798a-799a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

AB rAAV vectors have been shown to safely transduce hepatocytes in vivo, resulting in persistent and therapeutic levels of plasma human coagulation factor IX (hF.IX) in normal and hemophilia B animals. We have pursued pre-clinical safety and efficacy studies with the goal of developing a clinical trial. A recombinant **AAV** vector containing an alpha1-antitrypsin promoter and apolipoprotein E enhancer/hepatic locus control region (HCR) driving a factor IX minigene resulted in hepatocyte restricted gene expression and circulating hF.IX in the blood at apprx100% of normal physiological levels after intraportal administration in mice. rAAV transduction efficiencies and hF.IX expression levels were similar after portal vein or hepatic artery delivery but apprx2-5-fold lower when administered by peripheral tail vein in rats. A battery of safety studies in rats administered doses of up to 1 X 1013 vector genomes/kg via intrahepatic artery showed no toxicity. To determine the feasibility of delivery of rAAV into large animals by this route, 3 normal adult male dogs received apprx5 X 1012 vector genomes/kg of an **AAV**-null (non-functional expression cassette to avoid immune responses) vector by non-surgical, radiological-guided **infusion** into the hepatic **artery**. No vector related toxicity was observed. Serial semen samples collected over a period of at least 90 days were subjected to quantitative PCR analysis and found to be devoid of **AAV** vector genomes at a sensitivity of 100 vector copies per 300,000 haploid genomes. This suggests that the risk of germline transmission of vector delivered by an intravascular route is remote. Quantitative Southern analyses performed at least 90 days after vector administration, revealed apprx0.3 double-stranded genome copies per diploid genomic DNA equivalent in the liver, similar to that observed in previous rodent experiments in which therapeutic levels of hF.IX were observed. As a result of these preclinical studies, we have proposed a clinical trial, which is open-label, non-randomized, single administration with inter-patient dose escalation in design. The proposed starting dose is 50 to 100-fold less than the highest dose that was used in the toxicology studies, and the details of the study will be discussed. Our preclinical data indicate that intrahepatic delivery of rAAV vectors is safe, and likely to be therapeutic for the treatment of hemophilia.

L6 ANSWER 15 OF 16 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN

AU Svensson E C; Marshall D J; Woodard K; Lin H; Jiang F; Chu L I; Leiden J M (Reprint)

TI Efficient and stable transduction of cardiomyocytes after intramyocardial injection or intracoronary perfusion with recombinant adeno-associated virus vectors

SO CIRCULATION, (19 JAN 1999) Vol. 99, No. 2, pp. 201-205.
ISSN: 0009-7322.

AB Background-The delivery of recombinant genes to cardiomyocytes holds

promise for the treatment of a variety of cardiovascular diseases. Previous gene transfer approaches that used direct injection of plasmid DNA or replication-defective adenovirus vectors have been limited by low transduction frequencies and transient transgene expression due to immune responses, respectively. In this report, we have tested the feasibility of using intramyocardial injection or intracoronary infusions of recombinant adeno-associated virus (rAAV) vectors to program transgene expression in murine cardiomyocytes in vivo.

Methods and Results-We constructed an rAAV containing the LacZ gene under the transcriptional control of the cytomegalovirus (CMV) promoter (**AAV**(CMV-LacZ)). We then injected 1X10(8) infectious units (IU) of this virus into the left ventricular myocardium of adult CD-1 mice. Control hearts were injected with the Ad(CMV-LacZ) adenovirus vector. Hearts harvested 2, 4, and 8 weeks after **AAV**(CMV-LacZ) injection demonstrated stable beta-galactosidase (beta-gal) expression in large numbers of cardiomyocytes without evidence of myocardial inflammation or myocyte necrosis. In contrast, the Ad(CMV-LacZ)-injected hearts displayed transient beta-gal expression, which was undetectable by 4 weeks after injection. Explanted C57BL/6 mouse hearts were also perfused via the coronary arteries with 1.5X10(9) IU of **AAV**(CMV-LacZ) and assayed 2, 4, and 8 weeks later for beta-gal expression. beta-Gal expression was detected in <1% of cardiomyocytes at 2 weeks after perfusion but was detected in up to 50% of cardiomyocytes 4 to 8 weeks after perfusion.

Conclusions-Direct intramyocardial **injection** or **coronary artery** perfusion with rAAV vectors can be used to program stable transgene expression in cardiomyocytes in vivo. rAAV appears to represent a useful vector for the delivery of therapeutic genes to the myocardium.

L6 ANSWER 16 OF 16 MEDLINE on STN DUPLICATE 7
AU Lynch C M; Hara P S; Leonard J C; Williams J K; Dean R H; Geary R L
TI Adeno-associated virus vectors for vascular gene delivery.
SO Circulation research, (1997 Apr) 80 (4) 497-505.
Journal code: 0047103. ISSN: 0009-7330.
AB A variety of delivery systems have been used to genetically modify vascular endothelial cells and smooth muscle cells (SMCs), but currently available systems suffer from either inefficient in vivo gene transfer, transient episomal vector expression, or significant immune responses and inflammation. In the present study, we evaluated an alternate vector system, recombinant adeno-associated virus (rAAV) for transduction of vascular cells in culture and in vivo. Primary cultures of rabbit, monkey, and human SMCs; macaque and human microvascular endothelial cells; and human umbilical vein endothelial cells were efficiently transduced at a dose of 100 to 1000 DNase-resistant particles per cell. rAAV-mediated transduction of the vasculature in vivo was observed after intraluminal gene delivery or after intra-adventitial **injection** in carotid **arteries** of atherosclerotic cynomolgus monkeys. Whether vector delivery was intraluminal or adventitial, transduction was observed in the adventitia, particularly within microvessels (vasa vasorum) but not in cells of the intima or media. Transduction of adventitial microvessels was enhanced by balloon injury 4 days before gene transfer. This was particularly true for adventitial delivery. We have previously shown that adventitial cell proliferation increases significantly 4 days after balloon injury (45%) in this animal model. Together, these data suggest that cell proliferation may enhance **AAV** transduction in vivo in the vasculature. **AAV** vectors exhibited a tropism in vivo for the microvascular endothelium at the doses used in the present study, which may provide the opportunity for targeting gene delivery. In summary, we have demonstrated the utility of rAAV vectors for ex vivo vascular cell gene delivery and present an initial experience with rAAV for in vivo vascular gene delivery. This alternate vector system may overcome some of the limitations hampering the development of gene therapy for vascular disorders.

=> d au ti so 1-3 l7

L7 ANSWER 1 OF 3 MEDLINE on STN DUPLICATE 1
AU Iwatate M; Gu Y; Dieterle T; Iwanaga Y; Peterson K L; Hoshijima M; Chien K R; Ross J
TI In vivo high-efficiency transcoronary gene delivery and Cre-LoxP gene switching in the adult mouse heart.
SO Gene therapy, (2003 Oct) 10 (21) 1814-20.
Journal code: 9421525. ISSN: 0969-7128.

L7 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 2
AU Li J; Wang D; Qian S; Chen Z; Zhu T; Xiao X
TI Efficient and long-term intracardiac gene transfer in delta-sarcoglycan-deficiency hamster by adeno-associated virus-2 vectors.
SO Gene therapy, (2003 Oct) 10 (21) 1807-13.
Journal code: 9421525. ISSN: 0969-7128.

L7 ANSWER 3 OF 3 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN
AU Svensson E C; Marshall D J; Woodard K; Lin H; Jiang F; Chu L I; Leiden J M (Reprint)
TI Efficient and stable transduction of **cardiomyocytes** after intramyocardial injection or intracoronary perfusion with recombinant adeno-associated virus vectors
SO CIRCULATION, (19 JAN 1999) Vol. 99, No. 2, pp. 201-205.
ISSN: 0009-7322.

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